Welcome to FDA's
Public Workshop on the Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

January 8 and 9, 2015

Cara Tenenbaum, JD, MBA

Senior Advisor

Office of External Affairs

U.S. Food and Drug Administration

Topic 4: Notification and Adverse Event Reporting (MDRs)

- Will notification be adequate to provide FDA, laboratories, providers, patients, and other members of the public a comprehensive list of what tests are currently available for a specific intended use?
- Would it be sufficient to allow laboratory networks (i.e., more than one laboratory under the control of the same parent entity) that offer the same test in multiple laboratories throughout their network to submit a single notification for that test?

Topic 4: Notification and Adverse Event Reporting (MDRs)

- Are there certain types of LDTs for which the Agency should neither enforce requirements for registration and listing nor request notification in lieu of registration and listing?
- How can FDA leverage other information in the community to reduce the information collection associated with notification for laboratories while still obtaining sufficient information to inform the LDT classification and prioritization process?

Public Comment on Topic 4 Speaker #50

Elaine Lyon, PhD

ARUP Laboratories

Public Comment on Topic 4 Speaker #51

Mary Pendergast

Pendergast Consulting

Panel Discussion of Topic 4

Moderator: Maria Giovanni, PhD (NIH)

Panelists

- Clement McDonald, MD (National Library of Medicine)
- Christopher Newton-Cheh, MD, PhD (American Heart Association)
- Jan Nowak, MD, PhD (American Medical Association)
- Wendy Rubinstein, MD, PhD (NIH)
- Carrie Blout (National Society for Genetic Counselors)

Topic 5: Public Process for Classification and Prioritization

- How should FDA structure the advisory panels that will be convened to provide input to help FDA classify LDTs and prioritize them for enforcement of FDA premarket review requirements?
- Which stakeholders should be able to present relevant information or views at the panel meetings to discuss the classification and prioritization of LDTs?

Topic 5: Public Process for Classification and Prioritization

- What factors should be considered in determining LDT classification and risk?
- How should the advisory panel process weigh these factors when providing input for classifying LDTs and prioritizing LDTs for enforcement of FDA premarket review requirements?

Public Comment on Topic 5 Speaker #52

Edward Ashwood, MD

ARUP Laboratories

Public Comment on Topic 5
Speaker #54

Lawrence Hertzberg, MD

CSI Laboratories

Public Comment on Topic 5 Speaker #55

Gail Vance, MD

College of American Pathologists

Public Comment on Topic 5 Speaker #57

Paul Kim

Foley Hoag LLP

Public Comment on Topic 5 Speaker #58

Timothy Lynagh

Lyme Disease Association, Inc

Lyme & Other Tick-Borne Diseases: Process Concerns About FDA Testing Guidance

Public Process for Classification & Prioritization Section

Presented to
FOOD & DRUG ADMINISTRATION
Public Workshop-
Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) Jan. 8-9, 2015
NIH Campus, Bethesda, Maryland

Presented by
Timothy S. Lynagh
for
Lyme Disease Association, Inc.
www.LymeDiseaseAssociation.org

on
January 9, 2015

Lyme Disease Association, Inc. (LDA)

- Lyme Disease Association
  - Provides grants for research
    - Which has led to 35 peer reviewed science journal publications to date
  - Holds annual CME medical conferences for doctors and researchers
  - Is different than most other participants here, but shares a common interest with them
    - To ensure patient access to effective diagnostics & treatments

Issues Specific to Lyme Disease

- Controversy surrounding Lyme disease
  - Vested interest in tests
  - Quality of tests generally poor
  - Inconsistent test quality information even from government agencies
  - Agencies often say tests are sensitive while peer review often says otherwise
- All aspects of Lyme need to be questioned including the quality of tests and reliability of information – regardless of the source

Expert Panel Recommendations on Risks, Classification, Enforcement Prioritization

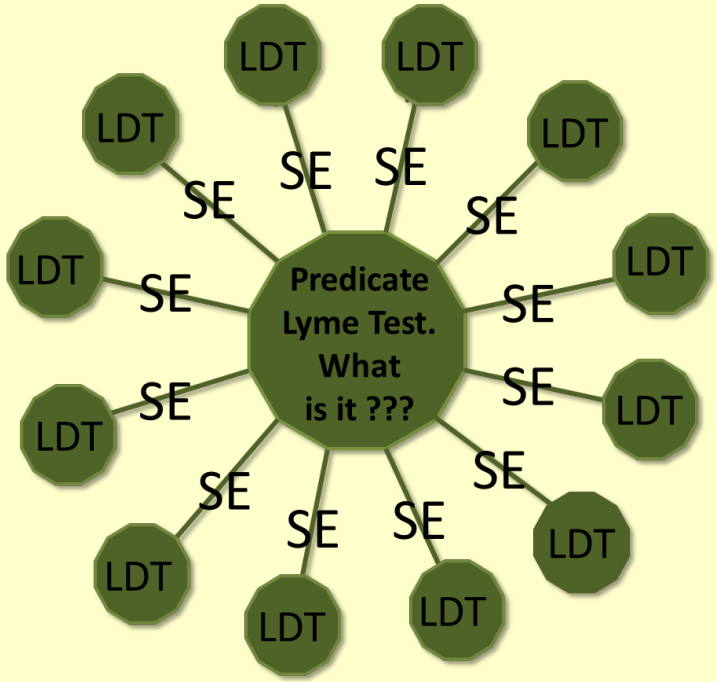
- Lyme has a history of bias of “experts”
  - Leads to concern about composition of panels
    - Screening of potential panel members for conflicts of interest
    - Representation of different perspectives to minimize bias

Risk Evaluation Concerns

- **Quality and efficacy of FDA-cleared Lyme tests are not well understood**
- **How do you evaluate risk if you do not have a good grasp on test performance?**

– Almost all FDA-cleared Lyme tests were based on substantial equivalence, which in the case of Lyme, sets a low bar

– For Lyme, we can't even identify what the predicate test was



SE-Substantially Equivalent
LDT-Laboratory Developed Test

Risk Evaluation Concerns

- Risk Communication on the Label
  - Labeling information should be evaluated with consideration given to prominently including, if not already provided
    - Information on purposes for which Lyme tests were developed
      - e.g., surveillance, screening or diagnosis
    - Limitations of tests
      - e.g., low sensitivity
    - Warnings regarding interpretation
      - e.g., a negative result does not necessarily mean that an individual does not have Lyme disease and further evaluation may be necessary

Risk Evaluation Concerns

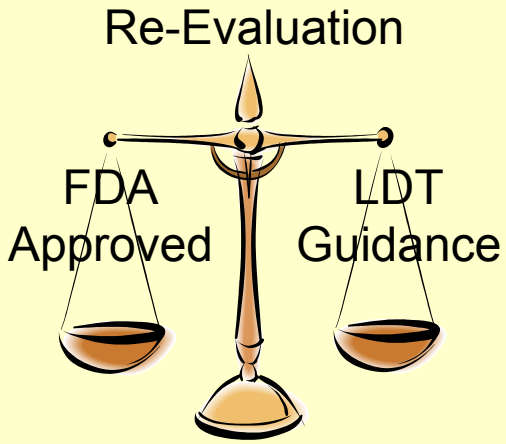
- The consequences of antibiotic use in Lyme need to be realistically evaluated, including consequences of delayed treatment
  - Needs to be a balanced assessment of consequences of false positives and false negatives
    - Excessive focus from some parties on adverse consequences of false positives, while minimizing patient and treating physician concerns with the serious health consequences of false negatives
  - Possible public health risks, such as the potential for development of antibiotic resistance, should not be misrepresented
    - Evidence does not support the use of antibiotics in Lyme as a significant contributor to the problem of resistance, contrary to frequent claims

Risk Evaluation Concerns

- Need to recognize that adverse events reporting for Lyme diagnostics is problematic
  - The existing adverse events system (MAUDE) has been very poor at identifying and capturing performance problems with cleared tests
  - Cannot even determine what specific tests were used by labs, since non-specialty labs often use >1 test
  - Issues regarding adverse events reporting for Lyme should be addressed simultaneously for FDA cleared tests and newly regulated LDTs

Evaluation of Risks - Conclusion

- Guidance necessarily focuses on LDTs that have not been subjected to FDA review
- In the case of Lyme diagnostics, tests previously cleared by FDA must be reevaluated
  - To level the playing field & protect patient interests
  - New public information requirements for LDTs should also be applied to existing FDA cleared tests if such information is not already available to the public



Thanks

- LDA thanks the FDA for the opportunity to present today at this testing guidance workshop

Lyme Disease Association, Inc.

national non-profit

www.LymeDiseaseAssociation.org

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732 938 7215 (fax)

Jackson, NJ 08527

Panel Discussion of Topic 5

Moderator: Barbara Zehnbauer, PhD (CDC)

Panelists

- Andy Fish (AdvaMedDx)
- David Flannery (American College of Medical Genetics)
- Len Lichtenfeld, MD (American Cancer Society)
- Amy Miller, PhD (Personalized Medicine Coalition)
- Gregory Storch, MD (Infectious Diseases Society of America)

BREAK

10:30 -10:50

General Public Comment Speaker #61

Curtis Hanson, MD

Mayo Clinic

General Public Comment Speaker #62

Amanda Jezek

Infectious Diseases Society of America

General Public Comment Speaker #63

Donald Karcher, MD

Association of Pathology Chairs

Donald Karcher, MD
President, Association of Pathology Chairs

Professor and Chair, Department of Pathology
The George Washington University Medical Center
Washington, DC

January 9, 2015

Laboratory Developed Tests (LDTs)

- Utilize scientific and clinical discoveries and technological innovation to offer clinical laboratory testing not otherwise available
- Typically developed at the request of, and in close collaboration with, clinical caregivers
- Fill important gaps in diagnosis and/or characterization of disease states

APC member departments want to ensure that . . .

- The technological and clinical innovation that is intrinsic to development of LDTs remains unhindered
- The quality and reliability of LDTs are maintained at the highest levels possible
- LDTs continue to be widely available for patient use

CLIA guidelines . . .

- Ensure that all lab tests, including LDTs, are accurate, reproducible, and reliable
- Require analytical validation of all lab tests prior to clinical use
- Require proficiency testing/inter-laboratory comparison for all analytes tested
- Require ongoing monitoring of the clinical validity of mod/high complexity test results

CLIA guidelines . . .

- Ensure that all lab tests, including LDTs, are accurate, reproducible, and reliable
- Require analytical validation of all lab tests prior to clinical use*
- Require proficiency testing/inter-laboratory comparison for all analytes tested*
- Require ongoing monitoring of the clinical validity of mod/high complexity test results

* Cessation of testing with poor performance

APC member departments support . . .

- Risk-based approach to oversight of LDTs
- Continued enforcement discretion for certain categories of LDTs
- Notification of FDA of LDTs performed by labs
- Medical device reporting (MDR) for LDTs
- Premarket review by FDA for the highest risk LDTs

APC member departments recommend . . .

- That CLIA guidelines continue to be the basis of quality, reproducibility, reliability, and clinical validity of LDTs
- For low and moderate risk LDTs, only . . .
  - Notification of FDA of LDTs offered
  - Reporting to FDA of suspected LDT malfunction (per the MDR requirement)
- For the highest risk LDTs, full FDA regulatory oversight, including premarket review

APC member departments recommend . . .

Definition of highest risk LDT

- Clinical consequences of incorrect result includes serious morbidity or mortality

AND

- Uses methodology based on proprietary, unpublished, and/or non-transparent testing algorithms, computations, and/or software, preventing inter-laboratory comparison or other independent verification of test results

Thank you!

For more information, please contact
Ms. Priscilla Markwood
pmarkwood@apcprods.org
(301) 634-7408

General Public Comment Speaker #64

Laura Koontz, PhD

Ovarian Cancer National Alliance

General Public Comment Speaker #65

Amy Miller, PhD

Personalized Medicine Coalition

General Public Comment Speaker #66

Federico Monzon, MD

Ivitae Corporation

General Public Comment Speaker #69

James Prescott, PhD

PathGroup

General Public Comment Speaker #70

Paul Radensky, MD

Coalition for 21st Century Medicine

General Public Comment Speaker #71

Parmjeet Randhawa

American Society of Transplantation

LUNCH BREAK

11:40 - 1:00

Topic 6: Quality System (QS) Regulation

- How can laboratories best leverage their current processes and procedures, implemented to meet CLIA accreditation requirements, to meet the FDA QS regulation requirements in the least burdensome manner?
- Are there FDA QS requirements that differ from CLIA requirements that FDA should continue not to enforce for laboratories that make LDTs?

Topic 6: Quality System (QS) Regulation

- What additional resources will laboratories need in order to assist them with implementation of the QS regulation?
- What is the appropriate timeframe for phase-in enforcement of QS regulation requirements in general and for design controls specifically?

Public Comment on Topic 6
Speaker #72

Andrea Ferreira-Gonzalez, PhD

Medical College of Virginia

Public Comment on Topic 6 Speaker #73

Nick Harris, PhD

IGeneX Inc.

Public Comment on Topic 6 Speaker #74

Vinod Jyothikumar, PhD

George Washington University

Public Comment on Topic 6 Speaker #75

Shinobu Kitamura, PhD

MBL International Corporation

Public Comment on Topic 6 Speaker #76

Liz Lison

Advocea LLC

FDA Public Workshop – Framework for Oversight of Laboratory Developed Tests (LDTs) January 8-9, 2015

Topic 6: Quality System Regulation

Liz Lison

ADVOCEA LLC

This presentation is based on my industry observations and personal opinions and does not necessarily reflect the actions or opinions of the companies I currently work with or have worked with in the past.

Introduction

- Describe specific challenges faced by laboratories in implementation of the Quality System Regulation (QSR)
- Propose how laboratories can best leverage their current processes and procedures, implemented to meet CLIA accreditation requirements, to meet the FDA QSR requirements in the least burdensome manner
- Comment on what is the appropriate timeframe for phase-in enforcement of QSR requirements in general and for design controls specifically

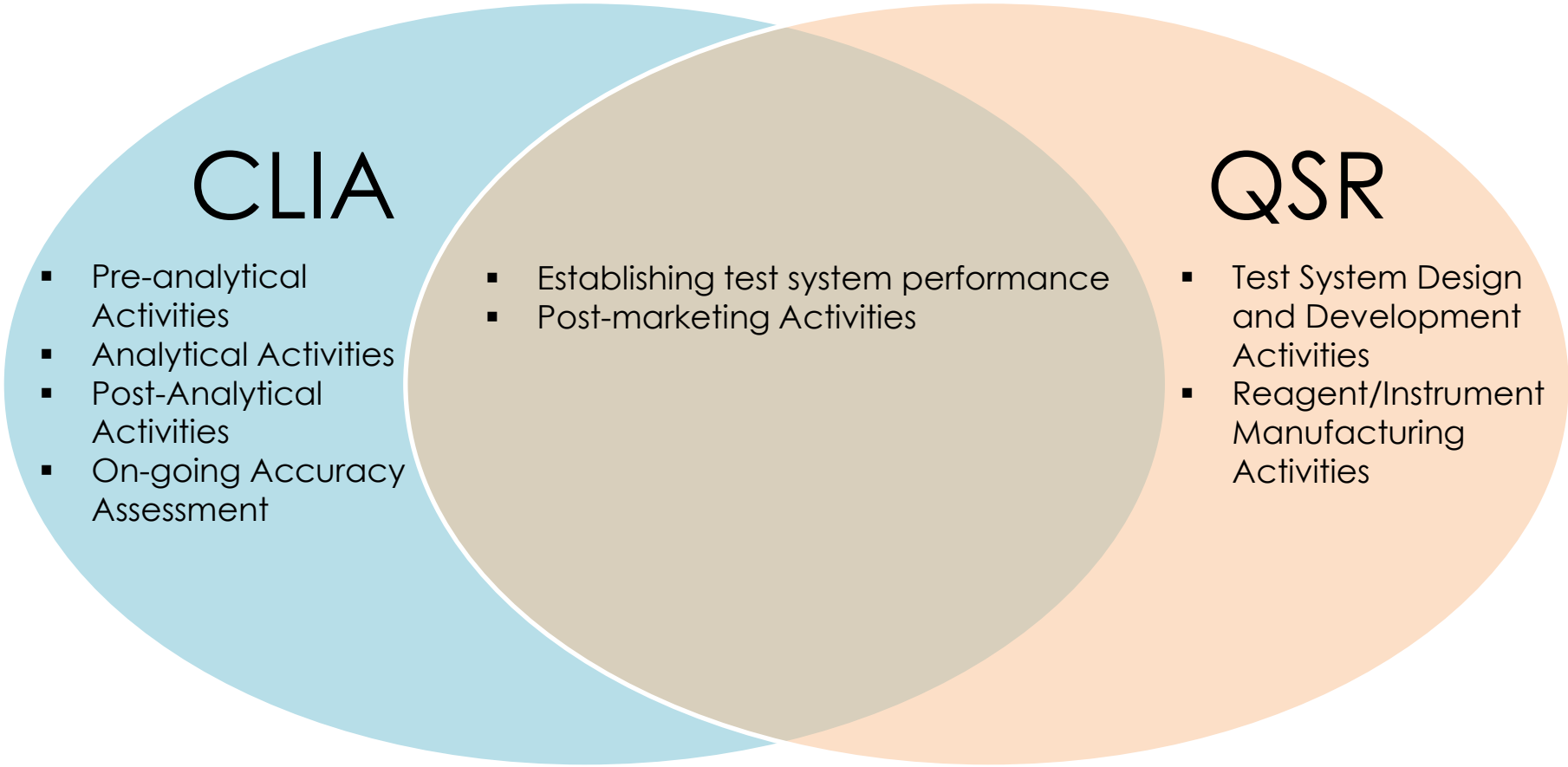
Challenges Implementing the QSR

- The QSR is confusing:
  - How does it apply to clinical laboratory testing?
  - What are Design Controls?
  - Do we need to have two quality systems?
  - It's so different from CLIA ……

Implementation of the QSR

Many <u>controls</u> in common so a single Quality System can address both regulations

How does the QSR Apply to Clinical Laboratory Testing?



Each Quality System controls different <u>activities</u>

Least Burdensome Integration of CLIA and FDA Quality Systems

Quality Manual/Quality Assurance Plan

DESIGN and MANUFACTURE (QSR)

Design Controls

Reagent Manufacture/Procurement

SAMPLE TESTING (CLIA)

Pre-Analytical/Analytical

Post-Analytical/Accuracy Assessment

POST-MARKETING (QSR)

Complaints

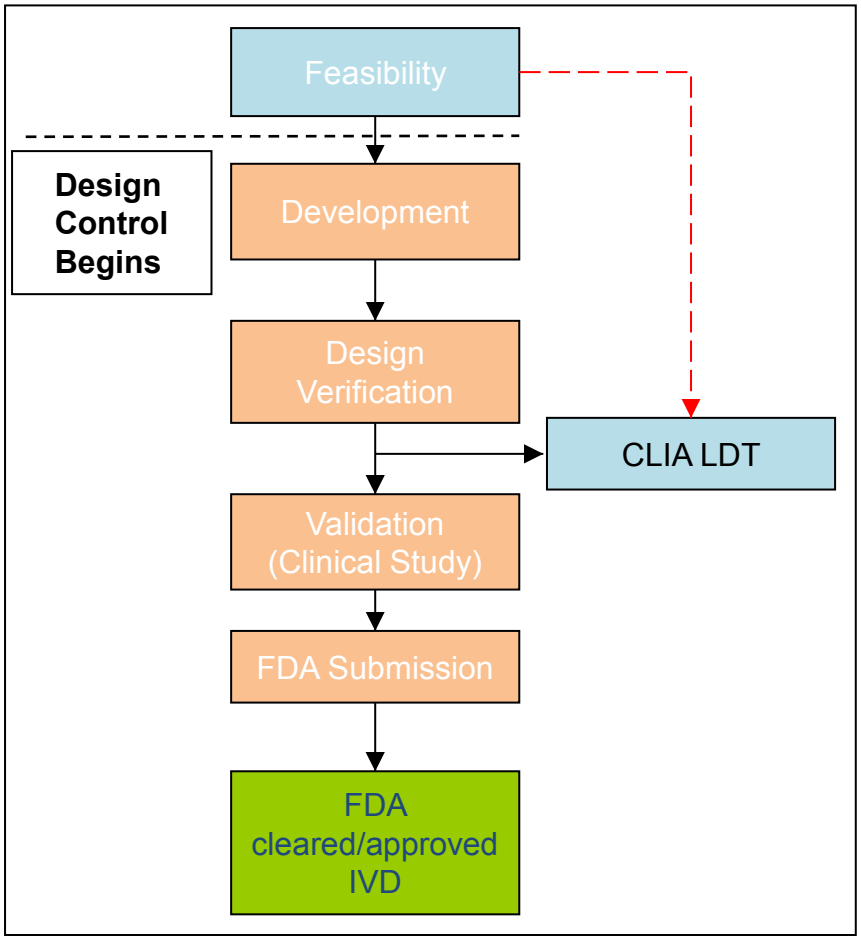
MDR

Common SOPs

Document and Record Controls/Equipment Qualification, Maintenance & Calibration/Training & Competency/Non-Conforming Events (CAPA)/Supplier and Materials Management/Facility Controls

Each Quality System is only applied to the activities it is designed to control

Phase–in of the QSR



- Requirements for compliance with the QSR should be independent of who has designed and developed the test
- Failures in LDTs are often related to lack of controls over QSR activities, especially lack of design controls
- For high risk tests enforcement of design controls should not be delayed for 24 months after publication of the guidance

Thank You

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Public Comment on Topic 6 Speaker #78

Robin Stombler

Microbiologics

Public Comment on Topic 6 Speaker #79

Katherine Tynan, PhD

Tynan Consulting LLC

Public Comment on Topic 6 Speaker #80

Sheila Walcoff

Goldbug Strategies LLC

Panel Discussion of Topic 6

Moderator: Larry Brody, PhD (NIH)

Panelists

- **Gail Vance, MD (College of American Pathologists)**
- **Andrew Hoofnagle, MD, PhD (University of Washington)**
- **Elaine Lyon, PhD (ARUP Laboratories)**
- **Scott Patterson, PhD (Amgen)**
- **Judith Wilber, PhD (CareDx)**
- **Mickey Williams, PhD (NIH)**

BREAK

2:30 - 2:50

General Public Comment Speaker #82

David Smalley, PhD

American Association of Bioanalysts

General Public Comment

On-Site Requests to Speak

Thank you for your feedback!

Docket Comments:

framework: http://www.regulations.gov/#!submitComment;D=FDA-2011-D-0360-0002

notification/MDR: http://www.regulations.gov/#!submitComment;D=FDA-2011-D-0357-0002

Questions: LDTframework@fda.hhs.gov